REMARKS/ARGUMENTS

By this Amendment, claims 3, 62, and 76 are amended. Claims 14, 48-50, and 72-75 have been withdrawn from consideration pursuant to a restriction requirement. Claims 3, 5-7, 9-14, 48-65, and 67-86 are pending.

Citations to the Specification are directed to U.S. Patent Application Publication No. 2005/0014254 (Kruse). Support for the changes to the claims can be found throughout the Specification as filed, and specifically: support for the limitation "removal of exocrine glandular tissue" can be found in original claim 19; support for the limitation "the tissue thus removed is divided in such a gentle way that cell structures in resulting tissue fragments are largely preserved" can be found in original claim 20; support for the limitation "the divided tissue is cultured in a culture medium that does not contain any additional growth factors or differentiation factors" can be found in original claim 8; support for the limitation "whereby most of the differentiated cells become detached from the stem cells, whereupon the stem cells adhere on a bottom of a tissue culture vessel' can be found in original claim 20; support for the limitation "the remaining tissue and nonadherent differentiated cells are largely separated by a first change of medium and the remaining nonadherent cells are separated by additional changes of medium at intervals of about 2 to 3 days" can be found in original claim 20.

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Reconsideration of the restriction requirement is respectfully requested.

Withdrawn Rejection

Applicant gratefully acknowledges the withdrawal of the anticipation rejection of claims 3, 5-7, 9-13, 51-56, 59, 62-65, 67-71, 76-81, 84 over Clarke, et al., 2000, Science, 288: 1660-1663.

Rejection under 35 USC § 103

Claims 3, 5-7, 9-13, 51-65, 67-71, 76-86 stand rejected as being obvious over Zulewski et al., 2001, Diabetes, 50: 521-533, Apte et al., 1998, Gut, 43: 128-133, and Pittenger et al., 1999, Science, 284: 143-147. This rejection is respectfully traversed.

With regard to the Zulewski reference, Applicant has previously pointed out that Zulewski describes nestin as a neural cell-specific stem cell marker (see e.g. abstract of the

Zulewski reference) and the isolated cells disclosed in Zulewski are merely multi-potent in so far as they are capable of differentiating into different pancreatic endocrine, exocrine and hepatic phenotypes, not pluripotent cells (see Response of March 9, 2010 at page 9). As evident for the skilled artisan, all those cell types are derived from a single germ layer, namely the endoderm, and the cells are not pluripotent adult stem cells.

The Examiner argues that regardless of what Zulewski et al. thought that their cells' developmental potential was based their expression of nestin, an artisan would have isolated and made clones of the cells from Zulewski et al. because at least they can be used to obtain pancreatic and hepatic cells. However, the claims are patentable over the combination of the Zulewski, Apte, and Pittenger references for the following reasons. The framework for the objective analysis for determining obviousness under 35 U.S.C. 103 is stated in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows: (A) Determining the scope and content of the prior art; and (B) Ascertaining the differences between the claimed invention and the prior art; and (C) Resolving the level of ordinary skill in the pertinent art. To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385 (CCPA 1970). MPEP 2143.03. It is important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.

Here, contrary to the Examiner's argument, the claimed composition of cells has been isolated by a method distinct from the method taught in Zulewski. The claims are directed to a composition consisting of isolated pluripotent adult stem cells obtained from an exocrine glandular tissue of a salivary gland, a lacrimal gland, a sudoriferous gland, a sebaceous gland and/or gastrointestinal tissue, wherein the exocrine glandular tissue originates from a mammal, wherein the process for producing the isolated pluripotent adult stem cells comprises: removal of exocrine glandular tissue; the tissue thus removed is divided in such a gentle way that cell structures in resulting tissue fragments are largely preserved; the divided tissue is cultured in a culture medium that does not contain any additional growth factors or differentiation factors,

whereby most of the differentiated cells become detached from the stem cells, whereupon the stem cells adhere on a bottom of a tissue culture vessel; the remaining tissue and nonadherent differentiated cells are largely separated by a first change of medium and the remaining nonadherent cells are separated by additional changes of medium at intervals of about 2 to 3 days; and isolating the pluripotent adult stem cells, further wherein the isolated pluripotent adult stem cells are capable of differentiating into cell types of all three germ layers in a culture medium that does not contain any additional growth factors or differentiation factors after culturing under spatial conditions which ensure three dimensional contact of the cells.

The claimed composition of cells has been made by a process distinct from the method as taught in Zulewski, because Zulewski used growth factors in the media. The Zulewski reference teaches that after digesting pancreatic tissue thoroughly washed islets are handpicked from the digest and suspended in modified RPMI medium, which was then transferred to tissue culture plates. Separation from adherent fibroblast cells and other non-islet cells was effected by subsequently (after 96 h) removing the supernatant with the islets and further cultivating the (once more) handpicked islets in the RPMI medium now supplemented with two growth factors. (Zulewski at page 522, column 1). From these islets, a monolayer of nestin positive progenitor cells (NIP) grew out and the cells from said monolayer were expanded in different media with various additives (most of them growth factors). (Zulewski at page 522, column 1). Thus, at least 2 growth factors were already present in the medium of the purified islet preparation from which the progenitor cells were derived when prepared according to the Zulewski reference. In contrast to this, neither the isolation medium nor the cultivation medium of the present method contains such growth factors, and no separation of islets from other cells takes place.

In addition, the Zulewski reference further teaches human nestin positive cells were placed in medium containing growth factors. (Zulewski at page 522, column 1, emphasis added):

> Cells in the monolayers—nestin-positive islet-derived progenitor (NIP) cells—were repeatedly recloned and expanded: 10 times over 8.5 months (rat) and 7 times over 8 months (human). In certain instances, human NIP cells were cultured in modified RPMI media containing 2.5 mmol/l glucose and in several growth factor combinations that include activin-A (2 nmol/l), hepatocyte growth factor (HGF) (100 pmol/l), or betacellulin (500 pmol/l). In other instances, NIP cells were challenged with nicotinamide (10 mmol/l), exendin-4 (10 nmol/l), activin-A, and HGF in media (11.1 mmol/l glucose) containing no serum.

This is in contrast to the claimed cell composition, which is cultured in media that does not contain any additional growth factors or differentiation factors.

In addition, the Examiner argues that while Zulewski does not specifically teach that their cells had potential to become other types of differentiated cells, as far as can be told, Zulewski's cells have the ability to differentiate into cell types other than pancreatic and hepatic because Zulewski's cells were obtained the same way as described in the specification. (Office Action at page 4).

However, the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' "In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Here, the Examiner has not met that burden by arguing that as far as can be told, Zulewski cells have the ability to differentiate into cell types other than pancreatic and hepatic. "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

If the Examiner is aware of, or alleges to have some knowledge that Zulewski's cells have the ability to differentiate into cell types other than pancreatic and hepatic, then the Examiner should provide such knowledge It would not be appropriate for the examiner to take official notice of facts without citing a prior art reference where the facts asserted to be well known are not capable of instant and unquestionable demonstration as being well-known. For example, assertions of technical facts in the areas of esoteric technology or specific knowledge of the prior art must always be supported by citation to some reference work recognized as standard in the pertinent art. In re Ahlert, 424 F.2d at 1091, 165 USPQ at 420-21. If applicant

adequately traverses the examiner's assertion of official notice, the examiner must provide documentary evidence in the next Office action if the rejection is to be maintained. See 37 CFR 1.104(c)(2). See also Zurko, 258 F.3d at 1386, 59 USPQ2d at 1697 ("[T]he Board [or examiner] must point to some concrete evidence in the record in support of these findings" to satisfy the substantial evidence test). If the examiner is relying on personal knowledge to support the finding of what is known in the art, the examiner must provide an affidavit or declaration setting forth specific factual statements and explanation to support the finding. See 37 CFR 1.104(d)(2).

In addition, the evidence of record suggests that the cells of Zulewski are not pluripotent, but are merely multipotent and only capable of differentiating into cells of the pancreatic lineage (Zulewski at page 531, columns 1 to 2, emphasis added):

> It remains unclear whether the NIP cells described in our studies are pluripotential stem cells, akin to bone marrow hematopoietic stem cells and neural ependymal stem cells, or are multipotential cells that can differentiate to more restricted cell lineages. Our speculation is that these intraislet cells are multipotential stem cells with the potential to differentiate into several pancreatic cell lineages (endocrine, exocrine, and ductal) or hepatic cell lineages (37–39) given exposure to appropriate environmental growth factor stimuli.

Thus, the Zulewski reference itself teaches that the cells are not pluripotent, but only multipotent and capable of differentiating only into cells of the pancreatic lineage.

The Examiner argues that Pittenger et al. and Apte et al. were cited to show how to obtain cells from the acini of pancreas (Apte et al.) and how to obtain a single cell from a mixture of cells (Pittenger et al.).

However, as set forth previously, the Pittenger and Apte references do not cure the deficiencies of the Zulewski reference because Pittenger et al. relates to the cultivation of mesenchymal stem cells and their capability to differentiate into several cell types derived from a single germ layer, namely the mesoderm, and Apte does not teach the isolation of pluripotent or even multipotent adult stem cells.

The combination of Zulewski, Apte, and Pittenger references do not teach or suggest a composition consisting of isolated pluripotent adult stem cells made according to the claims. Since none of the Zulewski, Pittenger or Apte references disclose or suggest these limitations, the combination of the references does not disclose or suggest these limitations, and therefore,

since the combination of the references does not disclose or suggest these limitations, there is no motivation to combine the references to reach these limitations, and no expectation of success.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

* * *

For at least the reasons set forth above, it is respectfully submitted that the above-identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

Should the Examiner believe that anything further is desirable in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

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Please charge or credit our Account No. 03-0075 as necessary to effect entry and/or ensure consideration of this submission.